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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
PRASTHOFER,T	
ART UNIT	PAPER NUMBER
1627	8

DATE MAILED: 05/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/421,422	HARBURY ET AL.	
	Examiner	Art Unit	
	Barba M. Koroma	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Please note the change in examiner prosecuting this application (see end of action).

2. Receipt is acknowledged of IDS, and request for extension of time, filed on 2/18/00 and 3/26/01 respectively, entered as paper numbers 4, and 6. The status of the claims are as follows:

3. Applicant's election of group I (claims 1-10) without traverse in Paper No. 7 is acknowledged.

4. Upon further consideration, examiner withdraws species election requirement.

5. Claims 1-14 are pending.

6. Claims 11-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 7.

7. Claims 1-10 are currently being examined in this application.

Claim Rejection 35 USC §112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 2, 3, 4, 5, 6, 8, 9, 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5, 6, 9 and 10 recite 'nucleic acid tags'. Even though the claims are drawn to 'methods of making a plurality of compounds', the language of the claims seem to suggest methods of tagging, making tags, or making compounds with tags. Clarification is requested.

Claim 1 recites 'first hybridization sequence' and 'second hybridization sequence'. The claim does not define what is meant by first and second hybridization sequence. The terms 'first' and 'second' may suggest a difference between the sequences based on significance, priority of association with other moieties, or order of occurrence on a given template. Clarification is requested.

Claim 1 recites 'a related reagent'. The term 'a related reagent' is confusing because it does not suggest what basis is being used to describe a reagent as related. Reagents could be related

based on a number of criteria such as physical state, pH, molecular weight, solubility, binding affinities, or composition. Clarification is requested.

Claim 2 recites the term 'solid phase reagents'. The term 'solid phase reagents' is vague and indefinite because it could mean any number of reagents such as those applied in solid phase combinatorial chemical synthesis, or to the class of regents generally referred to as 'solids'. Clarification is requested.

Claim 3 recites "conditions effective'. In chemical coupling, conditions that are considered effective range from moderate to highly effective. Without specifying what conditions are being described as effective, it would not be immediately clear to one skilled in the art what conditions are being referred to as 'effective'. Clarification is requested.

Claims 3, 4, 8-10 recite "for use" in method making claims. It is not clear whether the claims are directed to 'methods of use' or 'methods of making'. Clarification is requested.

Claim 5 recites 'until synthesis of the compounds is complete. What is considered complete synthesis is based on what is being synthesized in the first place. Since the claim only refers to what is being synthesized as 'compound', it is not clear what a state of completeness is, as claimed. Could it be a desired length, conformation, or sequence complexity? Clarification is requested.

Claim 8 recites 'desired compound activity'. Without defining what is considered 'a desired activity', it remains unclear what is meant by desired activity, especially because desired activity could vary from receptor binding specificity to pharmacologic inhibition, and gene activation. Clarification is requested.

10. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Claim 8 recites "enriching the plurality of compounds...identifying from said plurality of compounds, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags". The omitted elements are the method or process steps involved in identifying said compounds having a desired activity. Since the term 'identification' is synonymous with screening or selection, the steps involved must be included. Correction is requested.

11. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the steps or methods of 'synthesizing the compounds to completion'.

Claim Rejection 35 USC §112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 5 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids, does not reasonably provide enablement for other compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

Claims 1, 5 and 8 recite a "plurality of compounds". However, the specifications are not enabling with regards to synthesis of other compounds as stated in the claims, and as such, would require undue experimentation on the part of one skilled in the art to practice the invention as claimed.

The factors used in determining undue experimentation are as set forth In re Wands, 858 F.2nd 731, 8 USPQ2d 1400 (Fed. Cir 1988) and an undue experimentation analysis. See MPEP §§2164-2164.08(c). The factors to be considered include: quantity of experimentation necessary; the amount of guidance presented; the presence or absence of working examples; the nature of the invention; the state of the prior art; the predictability of the art; and the breadth of claims.

In order to practice the invention as claimed, one skilled in the art would be required to utilize a vast range of compounds outside the family of nucleic acids. This possibility constitutes an undue experimentation burden on the skilled artisan. The burden is worsened by the limited guidance in the specifications. For example, the specifications state "the present invention provides methods and compositions for the iterative synthesis and screening of a plurality of compounds wherein a nucleic acid tag directs and encodes the synthesis of the compound to which it is covalently attached, and the tag is a DNA molecule which can be amplified biochemically". However, because the description in the specifications were limited to nucleic acids, one skilled in the art would not be able to practice the invention as claimed. Further, the nature of the invention can be considered leading or cutting-edge technology, which has not received widespread application in the art. Thus, one skilled in the art would spend an excessive amount of time in an attempt to determine the applicability of other compounds to the instant invention as claimed. This situation is further complicated by the state of the prior art which is replete with numerous types of compounds synthesized and or utilized in combinatorial solid and liquid phase chemistry. The factors described above render the art unpredictable because it allows enormous variability in its applications to novel as well as well known compounds. While these issues already present overwhelming impediments to one skilled in the art, the open-endedness of the claim language make it an invitation to undue experimentation on the part of one skilled in the art to successfully practice the invention as claimed.

14. Claims 1, 2, 5, 6, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making nucleic acid compounds, does not reasonably

provide enablement for methods of tagging or methods of making compounds with tags. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

Since the specification specifically describes the process of making nucleic acids, in order for one skilled in the art to make other compounds, it would require an excessive amount of experimentation according to the Wand's factors, namely, quantity of experimentation necessary; amount of guidance presented; presence or absence of working examples; nature of the invention; state of the prior art; predictability of the art; and the breadth of claims.
The claim language seems to indicate that the invention is drawn to making tags or to a method of making compounds with tags. It would require burdensome experimentation in order to resolve the issue of what's being made, i.e. compounds with tags, or nucleic acid probes. The guidance in the specifications is limited to the process of making nucleic acids using DNA template or tags. This is contrary to the language of the claims which describe "the process of making tags, wherein the tags in each subset has as a selected one of a plurality of different first hybridization sequences, a mixture of different hybridization sequences". This is compounded by the absence of suitable working examples which describe the process of making tags and the process of making compounds with tags adds to the task which one skilled in the art will be faced with. Such lack of suitable examples suggest an enormous amount of experimentation in order to resolve the differences between the recitations of the claims and the disclosures of the specifications. The nature of the invention is rapidly evolving, and the state of the prior art is

dynamic. This suggests further that one skilled in the art cannot predict with certainty the pace of change, thereby making it difficult for one skilled in the art to substantiate the missing elements of the invention. These factors make it difficult to reliably ascertain to what degree applicants intend to facilitate the reproducibility of the claimed invention.

Claim Rejection 35 USC 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by **Brenner and Lerner (1992).**

Claims 1-10 are directed to a method of synthesizing a plurality of DNA-templated compounds and further identifying from said plurality of compounds, one or more with desired activity.

Brenner and Lerner disclose a process of alternating parallel combinatorial synthesis used to encode individual members of a large library of chemicals with unique nucleotide sequences. After the chemical entity is bound to a target, the genetic tag can be amplified by replication and utilized for enrichment of the bound molecules by serial hybridization to a subset

of the library. The nature of the chemical structure bound to the receptor is decoded by sequencing the nucleotide tag (abstract). Brenner and Lerner disclose a way of constructing 'encoded combinatorial chemical libraries', in which each chemical sequence is labeled by an appended "genetic" tag, itself constructed by chemical synthesis. In effect, a 'retrogenetic' way of specifying each chemical structure was implemented.

Two alternating parallel combinatorial synthesis processes are performed so that the genetic tag is chemically linked to the chemical structure being synthesized. In each case, addition of a monomeric chemical unit to a polymeric structure is followed by addition of an oligonucleotide sequence which is defined as "encoding" that chemical unit. The library is built up by the repetition of this process after pooling and division (These steps read on claims 1-7). The process involves the use of an appropriate linker attached to some solid-phase surface (page 5382, right column, step 1, lines 1-3). The use of a linker (synonymous with spacer reads claim 7). DNA strands with the appropriate polarity can then be used to enrich for a subset of the library by hybridization with the matching tags, and the process can then be repeated on this subset. Thus, serial enrichment is achieved by a process of purification, exploiting linkage to a nucleotide sequence that can be amplified. Finally, the structures of the chemical entities are encoded by cloning and sequencing the products of PCR (right column, page 5381, last paragraph, lines 1-11; page 5381, left column, lines 1-6). Brenner and Lerner disclose selection or identification or screening (page 5381, right column, lines 17-19, "each of the sequences is cloned in one phage and the relevant peptide can be elected by finding those that bind to the particular target", 3rd paragraph, lines 8-10, "active molecules are selected by binding to a receptor, and amplified copies of their retrogenic tags are obtained by PCR". This process reads

on claim 8. The sequences for the PCR primers must be chosen so that they do not occur within any coding segment and so that they can be readily removed from the final PCR product to avoid them dominating the selective hybridization process. This is achieved by building in sites for restriction enzymes with appropriate polarity of cutting. This process is consistent with and reads on the creation of reaction sites and partial digests of claims 9 and 10. This reference clearly anticipates the claimed invention.

16. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by **Lerner et al (US Patent No. 5,723,598)**

Claims 1-10 are directed to methods of synthesizing DNA-templated combinatorial libraries using nucleic acid tags which direct the synthesis of the compound library, and methods for identifying compounds with a desired activity.

Lerner et al teaches a way of combining the virtues of both chemical and genetic methods of constructing encoded combinatorial chemical libraries in which each chemical sequence is labelled by an appended "genetic" tag, itself constructed by chemical synthesis. The genetic tag is chemical linked to the chemical structure being synthesized, followed by the addition of an oligonucleotide which is defined to 'code' for that chemical unit, i.e. to function as the identifier of that of the chemical unit. The library is built up by repetitive of pooling and division (column 2, lines 48-63). An embodiment contemplates a method for identifying a chemical structure that participates in a pre-selected binding interaction with a biologically active molecule, where the chemical structure is present in the library (column 3, lines 27-32).

The strands of amplified copies can be used to enrich for a subset of the library by hybridization with the matching tags, and the process can then be repeated on this subset. Thus, serial enrichment is achieved by a process of purification, exploiting linkage to a nucleotide sequence which can be amplified. Finally, the structure of the chemical entities are decoded by cloning and sequencing the products of the PCR reaction. The invention contemplates a bifunctional unit according to the formula ABC, where A is a chemical moiety, B is a linker molecule, and C is an identifier oligonucleotide. The steps include; a) *admixing in solution the library of molecules to form a complex, b) isolating the complex formed, determining the nucleotide sequence of the polymer identifier, c) providing a linker molecule, d) conducting syntheses by adding precursor unit (reads on chemical reagents), e) repeating step b on one or more aliquots, and f) combining aliquots to form the library* (column 3, lines 1-60). Lerner et al teaches all the steps in claims 1-10, from DNA template library formation to screening of shuffled digest.

17. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by **Ruth (US Patent No. 5, 668,266).**

Claims 1-10 are directed to methods of synthesizing DNA-templated combinatorial libraries using nucleic acid tags which direct the synthesis of the compound library, and methods for identifying compounds with a desired activity.

Ruth teaches substantially pure single-stranded oligonucleotides having a preselected sequence of not more than about 200 nucleotides, atleast one of which is at a preselected position in the sequence and includes a base with a covalently attached linker arm containing or capable of binding atleast one reporter group or solid support (abstract). Ruth teaches that in one

embodiment of the invention, the single-stranded oligonucleotide has a substituent group or linker arm which has bound or is capable of binding a detectable reporter group or solid support. The *oligonucleotide is non-enzymatically synthesized by the step-wise addition of a selected reactive nucleotide monomer and a free hyroxyl-bearing terminal unit of an oligonuleotide chain of preselected sequence*, atleast one nucleotide of the completed chain having a substituent group bound or capable of binding atleast one reporter group or a solid support. This teaching of Ruth reads on 'synthesis', (claim 1), 'add substituent to chemical reaction site' (claim 4), 'synthetic step' (claim 5), PCR (claim 9) and 'producing new permutations of active compounds' (claim 10) as applied to nucleotide synthesis. The reference teaches reactive nucleotide monomers useful for the synthesis of the oligonucleotides. Such monomers contain an active phosphorus-containing group at the 5'- or 3'-hydroxyl of a ribonucleoside or deoxyribonucleoside, a linker arm attached to the base and bound and bound to or capable of binding a reporter group or solid support, and appropriate blocking groups on reactive sites. The incorporation of one or more such modified nucleotides into an oligonucleotide results in a modified oligonucleotide (column 4, lines 18-38). The nucleotide units in the modified oligonucleotide of the present invention can be purine or pyrimidine based, and can be ribonucleotides or deoxyribonucleotides. Such bases can take the form of purines, adenine, guanine, hypoxanthine, or of the pyrimidines, uracil, cytosine or thymine (column 4, lines 38-52). These teachings read on the modes of nucleotide synthesis of claims 1-10.

18. Claims 1-10 are rejected under 35 U.S.C. 102(e) as being anticipated by **Van Ness et al (US Patent No. 6,027,890).**

Claims 1-10 are directed to methods of synthesizing DNA-templated combinatorial libraries using nucleic acid tags which direct the synthesis of the compound library, and methods for identifying compounds with a desired activity.

Van Ness et al teach methods for detecting the binding of a first member to a second member of a ligand pair, comprising the steps of a) combining a set of first tagged members with a biological sample which may contain one or second members, under conditions, and for a time sufficient to permit binding of a first member to a second member, wherein said tag is correlative with a particular first member and detectable by non-fluorescent spectrometry, or potentiometry, b) separating bound first and second members from unbound members, c) cleaving the tag from the tagged first member, and d) detecting the tag by non-fluorescent spectromtry, or potentiometry, and therefrom detecting the binding of the first member to the second member (abstract). Van Ness et al teach methods and compositions for analyzing nucleic acid molecules, and more specifically, to the use of specialized tags and linkers which may be utilized to enhance sensitivity of the analyses of a wide variety of biological-based assays (column 1, lines 18-65). A wide variety of first and second member pairs may be utilized within the context of the present invention, including for example, nucleic acid molecules (DNA, RNA, nucleic acid molecules such as PNA, or any combination of these, proteins or polypeptides (e.g. antibody or antibody fragment, and binding partner such as a CDR, oligosaccharides, hormones, organic molecules and other substrates, or any ligand pair. Within various embodiments of the invention, the first and second members of the invention may be the same type of molecule or different types. For example, the representative first member second member ligand pairs include nucleic acid/nucleic acid molecule, antibody/nucleic acid molecule molecule, antibody/hormone,

antibody/xenobiotic, and antibody/protein. Preferably, the first member will recognize either a selected second member specifically or a class of related second member molecules (e.g. a class of related receptors). Preferably, the first member will bind to the second member with an affinity of atleast about 10-5/M. Within various embodiments of the invention, the nucleic acid probes and or molecules of the present invention may be generated by for example a ligation, cleavage, or extension (e.g. PCR) reaction. Within other related aspects the nucleic acid probes or molecules may be tagged at their 5'-end, and the so-tagged molecules function as oligonucleotide primers or dideoxynucleotide terminators. Within other embodiments of the invention, the bound first and second members, or exposed nucleic acids may be separated from unbound members or molecules by methods such as electrophoresis, capillary electrophoresis, micro-channel electrophoresis. In one aspect of the invention, a molecule of interest or precursor thereto is linked via a labile bond (or labile bonds) to a tag. Thus, compounds of the invention may be viewed as having the general formula: TLX, where T is the tag component, L is the linker component, that either is or contains a labile bond, and X is either the molecule of interest (MOI) component or a functional group through which the MOI may be joined to T-L (columns 2, line 20-65). This reference reads on the recitations of the claims 1-10, with regards to the synthesis of nucleic acids using DNA templates, referred to in the instant invention as tags.

18. No claim is in condition for allowance.

19. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

20. All inquiries pertaining to this case should be directed to ***Barba M. Koroma.*** This examiner can normally be reached at: **703 305 1915, at *9:00am to 5:00pm, Monday through Friday.***

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, PhD, can be reached at: 703 308 2439. The phone number for the organization where this application or proceeding is assigned is: 703 308 2742. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is: 703 308 1235.

Barba M. Koroma, Ph.D
Patent Examiner
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May 3, 2001

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